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ENDOSCOPIC LASER FORAMINOTOMY. G. David Casper, M.D., 1016 S.W. 44th Street, Oklahoma City, Oklahoma 73109; James E. Stoll, M.D., 2015 E. Newport Avenue, Ste. 605, Milwaukee, WI 53211. Symptomatic exit zone foraminal stenosis occurs due to a combination of pathologic conditions. Degenerative disc bulging, segmental instability with secondary osteophytes at the foramen or facet joint, facet hypertrophy, degenerative invagination of the ligamentum flavum, and lateral lysthesis may all combine to encroach upon a nerve root as it passes through the intervertebral foramen. Typically, these patients are elderly with spinal conditions and comorbid medical conditions which make them less than optimal surgical candidates. With the development of foraminal endoscopic epidural surgery, an approach became available to visually address the pathology with minimal surgical morbidity. The procedure is performed utilizing an endoscopic device with a 2.1 mm working channel which accommodates a 90 degree side-firing laser fiber. The purpose of this paper is to present procedural specifics and clinical follow-up data on 10 patients with foraminal stenosis treated utilizing this approach. All patients exhibited signs and symptoms of lumbar radiculopathy which was isolated to a single root. Patients had leg pain equal or greater than back pain which was unrelieved by conservative measures including PT, oral NSAIDs and epidural steroid injections. All patients underwent MRI or discogram with or without CT. Patients with herniated discs or central stenosis were not included in the study. Postoperatively, patients were evaluated by an independent interviewer and results based upon modified Macnab criteria. Overall success rate for the group is 100 percent, with a minimum follow-up of 8 months and an average follow-up of 17 months. Endoscopic foraminal decompression represents a minimally invasive procedure in a carefully selected population of patients with foraminal stenosis. The addition of laser energy as a debridement tool expands treatment options for both bony and soft tissue pathology.

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RESULTS OF A PROSPECTIVE CLINICAL TRIAL OF THE HOLMIUM:YAG LASER IN DISC DECOMPRESSION UTILIZING A SIDE-FIRING FIBER: FOUR YEAR FOLLOW-UP. G. David Casper, M.D., Orthopaedic Surgeon, 1016 S.W. 44th Street, Oklahoma City, Oklahoma 73109.

223 patients who met inclusive criteria were entered into this study of the Ho:YAG laser with side-firing fiber. This study was designed to evaluate and report procedural specifics and long-term follow-up results for patients having received disc decompression with this operative modality.

Patients were evaluated by an independent interviewer immediately postoperatively, at three months, six months, one year and annually thereafter. Ratings are based on the Modified Macnab Criteria.

All patients presented with radicular leg pain, with or without back pain, which had not responded to at least six weeks of non-operative care; including rest, NSAID, physical therapy or epidural steroid injections. Each met AAOS criteria for surgical intervention. Patients with central spinal stenosis, lateral recess stenosis or sequestered discs were not considered for this study.

Postoperative follow-up at four years yielded a surgical success rating of 82 percent. Results of LADD suggest that this procedure is a viable surgical alternative for the treatment of select lumbar disc disorders.

OTOLARYNGOLOGY/ PULMONARY

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MUCOSAL INTACT LASER TONSILLAR ABLATION: DOSIMETRY STUDIES

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Previous research conducted at this laboratory has shown that tonsillar tissue can be made to regress completely following mild heating by irradiation with the 805 nm diode laser. In preparation for a limited pilot human clinical study, further histological and dosimetric animal model experiments have been performed using the 805 nm diode laser. The objective of this experimentation was to explore the safety and effectiveness of a range of laser powers and irradiation times, to determine optimal therapeutic values. In the first set of experiments, the total laser energy delivered to the tissue was held constant, and the minimum laser power consistent with complete tonsillar atrophy was determined. Then, with the laser power fixed, the exposure time was varied to determine the minimum total energy required for optimal results. Temperature measurements taken during irradiation of the tonsils with the various laser parameters were correlated with outcome. In addition, the effect of inflammation and hypertrophy of the tonsils on the outcome of the procedure was observed in an animal with experimentally-induced tonsillitis. Results showed that a wide range of laser parameters (7 to 11 W) may be used to cause significant shrinkage of the tonsils with no damage to surrounding structures. Laser parameters in the therapeutic range for normal tonsils also cause significant shrinkage of enlarged and inflamed tonsils. The results of this study continue to support the expected benefits of reduced morbidity and lower costs for the clinical procedure.

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Neodymium-YAG laser treatment for recurrent carcinomas of the oral cavity. Marcos B. Paiva, Romaine E. Saxton, Keith Blackwell, Thomas Calcaterra, Ana Amelia P. Paiva, Jacques Soudant, Adrien A. Eshraghi, Dan J. Castro.
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The objective of this study was to review different aspects and results on Nd:YAG laser photo-thermoablation for palliation of recurrent tumors of the oral cavity.

METHODS: Seventeen patients were treated with the Nd:YAG laser between July 93 and July 96 (9 male and 8 female). The laser output was 50W and 1064nm infrared light was delivered through a curved oral handpiece (power density=750 J/cm^2). A total of 25 tumors average size=10.4cm^3 were treated (range: 0.5-43cm^3).

RESULTS: Twelve patients had no evidence of recurrence on average follow up of 22 months (range = 2 - 36). One patient had no response to therapy and four patients remained biopsy positive or had a visible tumor recurrence after therapy. Stratified by tumor site

Nd:YAG treatment led to complete response in 3/3 oral mucosa, 2/2 tongue, 3/3 gengiva, 2/2 floor of mouth, 4/7 palate, 3/3 retromolar trigone, 0/2 base of tongue and 3/3 oropharynx. The procedure was well tolerated in most cases and was repeated at intervals in patients with recurrences for a total of 52 laser treatments (average 3.2 treatments/patient).
CONCLUSION: Nd:YAG treatment of recurrent oral cavity cancer can be performed safely and tumor ablation by laser leads to palliation in most cases with improved function and reduced pain.. However, extended follow-up is needed before convincing evidence of long-term therapeutic benefits is obtained.

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AVOIDING COMPLICATIONS OF WRAPPED RED-RUBBER ENDOTRACHEAL TUBES IN LASER AIRWAY SURGERY

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Purpose: To demonstrate the dangers inherent in wrapped endotracheal tubes for laser airway surgery and offer management suggestions to avoid complications.

Methods: Intra-operative endoscopic photographs and post-operative display of unravelled, exposed endotracheal tube with resultant foil particles in hypopharynx are presented. Intra-operative management is detailed through endoscopic images.

Results: Wrapped red-rubber endotracheal tube is demonstrated to unravel, leaving shredded metal wrapping in hypopharynx. Intra-operative management of this complication successfully avoided tube fire during laser airway surgery, allowing safe debulking of obstructing supraglottic carcinoma.

Conclusions: The wrapped endotracheal tube must be used with caution in laser airway surgery. Tube insertion or manipulation of the laryngoscope can cause the wrapping to unravel, both exposing the flammable tube and leaving metallic wrapping as a foreign body that can result in airway obstruction. Pre- and intra-operative confirmation of the integrity of the foil wrapping along with survey of hypopharynx following tube removal for retained metallic foil is recommended. The use of saline-moistened cottonoids may be used to protect an exposed tube during limited periods of laser airway surgery.

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ND-YAG LASER ENDOSCOPY FOR TREATMENT OF SEVERE SUPRA AND SUBGLOTTIC STENOSIS.

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Purpose: A combined approach for treatment of complex subglottic obstruction has being proposed. The supra glottic lesion was treated using steroids locally, and then the subglottic area was treated w/ Laser Endoscopy a. endotracheal stent .
Methods: Prolonged intubation caused severe damage to supra and subglottic area, that lead to a cardiac arrest, obliding an urgent tracheostomy. Patient was referred to a Lasertherapy, due to progressive dyspneia, recurrent infections a. bleeding. Neck CT scan reveled an intense obstruction 85% upper third of trachea, which extended for 2.8 cm and the a massive edematous tissue of the supra glottic region. The supra glottic area was infiltrated with steroids. The O2 sat. % was 92% previous to the surgery and after 99%. Pre-procedure the supra glotic area was inspected a. assured to be permeable. Under general anesthesia, the endoscopic (rigid bronchoscopy) photoressection with Nd-YAG Laser (30 W, 0.5 sec) of the granuloma a. the scar tissue in the sub glottic region was carried out for several hours, successfully.
Result: An excellent lumen was achieved, although it was necessary to insert an endotracheal protese (16/5 cm Dumon stent). To place a. keep stent on the upper third of the trachea; thereby we devised a technique by which high tracheal stent could be sutured and fixed externally during endoscopic placement. There were no incidente during or after the procedure.
Conclusion: The expiral scan of the neck demonstrated that the stent was bellow 18 mm of the true vocal cord, restore the voice, secure the airways, no interferance with deglution function. High doses of steroids are maintained in the first month, reducing through the following months, in order to preventing inflammatory granulation tissue formation.

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TEMPERATURE DISTRIBUTION AND TISSUE NECROSIS FOLLOWING EXPOSURE TO INTERSTITIAL Nd:YAG LASER LIGHT

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Introduction: Interstitial Nd:YAG laser light applications find their way to clinical practice among others in therapy of voluminous hemangiomas and voluminous vascular malformations, in selected cases also for palliative treatment of recurrent malignomas of the head and neck. **Material and Methods:** Direction of the temperature emission was evaluated with an egg white model. To evaluate the temperature distribution of Nd:YAG laser light in tissue, experiments with 26 livers, spleens and tongues of alltogether 30 normal, healthy and adult pigs were performed. Organs were taken immediately after the animals had been sacrificed. Four temperature probes were inserted into the tissue around the laser fiber. The course of the change in tissue temperature was measured by a computing unit. Four different fiber types were used (bare fiber, ring-mode-fiber, side-fiber, diffuse fiber). All fibers had a diameter of 600 µm. The size of the coagulation necrosis was evaluated macroscopically as well as in histologic sections. **Results:** Each fiber type showed a characteristic pattern of temperature emission in organ tissue. The size of the tissue necrosis showed a linear correlation to the applied laser powers. The diameter of necrosis could not be increased once it had reached a certain extent. **Conclusion:** The results of the presented study indicate that the treatment of defined areas of tissue is possible by interstitial Nd:YAG laser therapy. Every fiber type shows its charcteristic pattern of tissue denaturation. To achieve honogeneous zones of coagulation the use of low powers over a long exposure time is recommended.

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INVESTIGATIONS TO THE REGENERATIVE FEATURES OF CULTIVATED SQUAMOUS CELL CARCINOMA CELLS FOLLOWING LASER SURGICAL INCISIONS

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Introduction: This study was initiated to clarify, whether the morphologic changes in squamous cell carcinoma cell (SCC) lines after laser incision correspond to the changes that are observed after incisions on mucous membranes of the upper aerodigestive tract (UADT). The second question to be investigated was the correlation between the impact of laser energy density on the cells and the period of time until the resulting defect was overgrown by viable carcinoma cells. **Material and Methods:** Two SCC cell lines (UM-SCC-11B and HCFMK-1) were seeded in Petri dishes of 5 cm diameter. Incisions with the CO_2 laser were performed at a distance of 400 mm with laser powers ranging from 1-8.5 Watt under reproducible conditions. Morphologic changes were registred daily under inverse light microscopy and documented by photography. **Results:** The thermic damage induced by the CO_2 laser were according to the laser energy density of varying extent. Applications of 1 Watt already induced a destruction of the monolayer that was macroscopically visible. Applications above 3 Watt led to a thermic damage of the Petri dish. With increasing laser energy density the zone of coagulation and necrosis became broader and more obvious. The resulting defects showed the same histologic structure that can be observed after incision on the mucous membranes of the UADT. All resulting defects were again overgrown by carcinoma cells. The time until closure was achieved ranged from 1 day after 1 W to 22 days after an 8.5 W incision. **Conclusion:** Laser tissue effects can successfully be studied on in vitro models of SCC of the UADT. It shows that viable SCC cells can migrate over incisions after laser surgery, which might contribute to understanding of local recurrence.

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DOES SURGERY WITH LASERS HAVE AN INFLUENCE ON p53 DETECTION IN RESECTION MARGINS OF CARCINOMAS OF THE UPPER AERODIGESTIVE TRACT (SCC of UADT) ?

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Background: There seems to be a correlation between the proof of the p53 protein in the margins of excised carcinomas and a higher incidence of recurrences [Koch, 1996]. The presented study was initiated to clarify whether p53 protein can be detected in the resection margins of lasersurgically excised tumors despite the high temperatures induced by the laser light. **Material and Methods:** Healthy mucosa of the oropharynx was excised with the scalpel, the CO_2 laser and the Nd:YAG laser (n=28). Detection of wild-type p53 was performed by immunohistochemistry, the ELISA technique and amplifications of exons 4 and 5 of the p53 gene. SCC of UADT (n=19) were excised with the same cutting devices as mentioned above and the occurence of p53 in the margins was determined by immunohistochemistry and ELISA technique. **Results:** The expression of p53 could be detected in all mucosa specimen by ELISA. In lasersurgically excised tissue regularly a zone adjacent to the resection margin could be demonstrated where p53 was not evident. Quantitative differences were evident depending on the mode of excision and detection. By ELISA an overexpression of p53 could be shown in 14 of 19 (73.7%) carcinoma specimen, by immunohistochemistry only in 10 of 19 (52.6%) specimen. **Conclusion:** On immunohistochemistry lasersurgery does only inhibit the detection of p53 in a narrow zone of necrosis. The ELISA test is sensitive enough to detect p53 overexpression in resection margins after laser surgery that were immunohistologically negative. Laser surgical resection should therefore be no obstacle for the definition of tumor free margins, at least if molecular biologic methods are employed.

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LASER LABYRINTHECTOMY FOR INTRACTABLE VERTIGO

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Objective: The goal of this study was to gain the possibility of the Argon Laser for the inner ear surgery. Especially for the patients complaining of intractable vertigo with serviceable hearing.

Patients and Methods: Three patients with intractable vertigo were operated with Argon Laser. After stapedectomy Argon Laser was irradiated through the oval window to the otolith organ. Oval window was sealed with perichondrium and ossicular chain was reconstructed with teflon piston attaching to the incus.

Results: Vertigo disappeared on two patients. Hearing was preserved. Hearing was deprived on one patient who needed total labyrinthectomy.

Conclusion: Argon laser seems to become a useful tool in inner ear surgery.

PHOTODYNAMIC THERAPY/ONCOLOGY

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MONTE CARLO SIMULATION OF LIGHT FLUENCE IN A CYLINDRICAL HOLLOW ORGAN: INFLUENCE OF OPTICAL AND GEOMETRICAL CHARACTERISTICS.

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The propagation of light emitted by a linear diffuser placed in a cylindrical cavity has been investigated by means of a Monte Carlo (MC) method. Tissue optical parameters (μ_a, μ_s, g, n_{12}), dimensions of the cavity (height and radius), as well as light diffuser characteristics (length, emission profile and emitted power) are required as input data by the MC code. To establish the effects that tissue optics and geometrical characteristics play in tissue light penetration, a series of MC simulations were carried out. At a fixed reduced scattering coefficient (μ_s'), μ_a was varied from 0.1 to 5 cm^{-1}

and, conversely, at a fixed μ_a, μ_s' was varied from 2.5 to 50 cm^{-1}. Different cavity radii (from 0.5 to 2.0 cm) were considered. Since in clinical practice, i.e. in a PDT treatment, light dosimetry is performed on the basis of the so-called non-scattered fluence rate, Φ_{ns}, results had been referred to that parameter. At μ_a=0.1 cm^{-1}, the depth where fluence rate is equal to Φ_{ns} varies from 0.61 to 0.68 cm by changing μ_s' from 2.5 to 50 cm^{-1}, whereas, at μ_s'=25 cm^{-1}, it varies from 0.04 to 0.78 cm by changing μ_a from 0.1 to 5 cm^{-1}. As regards the maximal fluence rate in depth (Φ_M), the ratio Φ_M/Φ_{ns} varies, at μ_a=0.1 cm^{-1}, from 6 to 18 by changing μ_s' from 2.5 to 50 cm^{-1}, and, at μ_s'=25 cm^{-1}, from 1.7 to 13.1 by changing μ_a from 0.1 to 5 cm^{-1}. By increasing the cavity radius, a shift in the isofluence curves is being expected along the cavity axis, which is mainly due to the anisotropy in the photon angular emission of the cylindrical fiber. These data suggest that light dosimetry in PDT should be performed very carefully and the uncertainties in the estimate of the actual optical parameters of tissue *in vivo* have to be taken into account.

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PHOTODYNAMIC DESTRUCTION OF *HAEMOPHILUS PARAINFLUENZAE* AND *STAPHYLOCOCCUS AUREUS* BY ENDOGENOUSLY PRODUCED PORPHYRINS

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Bacterial resistance against antibiotics is an increasing problem in medicine. This stimulates study of other bactericidal regimens, one of which is Photodynamic Therapy(PDT). It has already been shown that various Gram-positive and Gram-negative bacteria can be killed by PDT in vitro, using exogenous sensitizers. An alternative way of photosensitizing cells is to enhance the production of endogenous porphyrins.

In the underlying in vitro study bacterial survival and porphyrin production is studied of *H. parainfluenzae* and *S. aureus*, after sensitization by incubation with an excess of δ-aminolaevulinic acid(ALA) and subsequent illumination.

H. parainfluenzae, incubated with increasing amounts of ALA showed decreased survival after irradiation with 630 nm light. Of various wavelengths, 617 nm appeared to be the most efficient in killing the bacteria. Destruction of *S. aureus* under comparable conditions was evidently more limited.

The produced porphyrins of both bacterial species showed spectrophotometrically a maximum at 617 nm, with a much lower peak at 680 nm. Methicillin-resistant strains of *S. aureus* produced less porphyrins than the sensitive strains. In conclusion killing of *H. parainfluenzae* and to a lesser extent of *S. aureus* could be achieved in vitro, after endogenous sensitization with ALA.

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SC102 MEDIATED INTRA-ABDOMINAL PHOTODYNAMIC THERAPY IS SAFE FOR COLORECTAL CANCER.

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Purpose: To study the safety of Adjuvant Intraoperative Photodynamic Therapy (AIOPDT) for colorectal cancer using the new photosensitiser SC102 in a large animal model.

Methods: A dose of 4.4 μmol kg^{-1} of *SC102* produces tumour necrosis equivalent to clinical doses of *mTHPC* in a murine model. This dose of *SC102* was given iv to 12 pigs. Laparotomy was then done after seven or fourteen days and abdominal structures, including colonic anastomosis, were exposed to 652nm laser light at a dose of 20 or 50 Joules cm^{-2}. Paired structures within each animal acted as controls. Terminal laparotomy was done after a further 8 or 42 days for assessment of damage by inspection and physiologic assessment, and by histology.

Results: Colonic anastomoses healed normally. Mean bursting pressures of anastomoses were 253 mmHg (range 160-280) in controls and 250 mmHg (range 160-280) in treated anastomoses (12 in each group). There was no significant difference in observed pressures during Whitaker's tests for patency between control and treated ureters (t-test, P=0.007). Other abdominal structures including stomach, small intestine, urinary bladder, iliac vessels on histology showed only mild damage which is unlikely to affect function.

Conclusions: Adjuvant treatment of colorectal cancer appears to be safe using *SC102* at a potentially effective dose. If efficacy is confirmed by clinical studies, this new photosensitiser may help to reduce loco-regional recurrence of the disease following curative resection.

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BIOREDUCTIVE CYTOTOXIN-ENHANCED LASER MICROVASCULAR TARGETING

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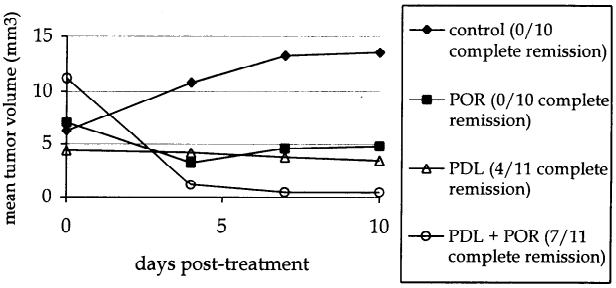
Vascular targeting is an approach to cancer treatment that takes advantage of the interdependence of proliferating tumor cells and pathologic neovasculature. Here, the use of a bioreductive agent preferentially toxic to hypoxic cells is investigated as a means of augmenting tumor cell kill resulting from photothermal destruction of tumor microvasculature.

Tumors were produced in the cheek pouches of hamsters by transplantation of human squamous cancer cells. Hamsters were divided into 4 treatment groups: (1) control, (2) bioreductive agent porfiromycin only (POR), (3) 585 nm pulsed dye laser only (PDL), and (4) combined PDL and POR. Results of a single treatment on mean tumor volume are shown in the figure below.



These data indicate that tumor regression and remission following laser vascular targeting may be enhanced by administration of a bioreductive cytotoxin.

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COMPARISON OF PULSED FLASHLAMP PUMPED DYE AND QUASI-CW LASER IRRADIATION FOR PDT AT 630NM

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Lightsources for PDT have been traditionally dye lasers pumped by argon ion or frequency doubled Nd:YAG lasers. These in most cases very spacious lasers present well known problems of low efficiency and calibration, some of them are tunable to different wavelengths. Recently diode laser reached the market with different wavelengths above 630nm for the use with new photosensitizers, but as the wavelenght is fixed, several lasers are necessary for the use with different photosensitizers and currently none is currently available with an emission at 630nm, the most important wavelength for hematoporphyrin derivates.

During the last 12 months a new flashlamp pumped dye laser (630nm, 80µs, 1-10Hz, Emax 1J/p) was evaluated in comparison with a common KTP-pumped dye laser. The generation of 1O2 was measured with ESR. From July 1996 to July 1997 41 treatments at more than 200 lesions in 32 patients were done for benign and malignant diseases. 85 lesions in 14 patients were irradiated with the pulsed dye laser, 4 patients were treated with both lasers at the same time in different areas.

The generation of 102 was equivalent to quasi-cw lasers and correlated with the energy emitted. In clinical use a simultaneous reaction was seen in all patients with simultaneous irradiation of both lasers. Treatment times were significantly shorter with the pulsed dye lasers as the power could be increased without significant warming of the area or pain reception by the patients.

The flashlamp pumped dye laser at 630nm shows equivalent qualities for PDT as currently available laser systems. It's use is simple and treatment times are shortened.

Datas will be updated.

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COMPARISON OF CUTANEOUS PHOTOSENSITIVITY OF *MTHPC* AND A POLYETHYLENE GLYCOL DERIVATIVE (SC102)

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Purpose: To compare the extent and duration of skin photosensitivity after administration of a new soluble polymer photosensitiser for photodynamic therapy with *metatetrahydroxyphenylchlorin (mTHPC)*.

Methods: *mTHPC* was given intravenously to two pigs at 0.31 µmol kg^{-1} and *SC102* was given to fifteen pigs at 4.4 µmol kg^{-1}. Following administration of the drugs, areas of shaved skin of the back of these animals were exposed to light from a tungsten lamp with a daylight filter producing about 100 mW cm^{-2}, approximately twice the intensity of the midday summer sun in California. Duration of exposure was from 2 minutes to 16 minutes. The response of the skin to light was assessed by inspection after 30 minutes, 3, 6 and 24 hours and then daily until the response either totally disappeared or became a permanent scar.

Results: Cutaneous photosensitivity due to *mTHPC* appeared 6 hours after administration and lasted 10 days whereas sensitivity due to *SC102* was observed from 24 hours to 24 days. The maximum sensitivity of the skin due to *mTHPC* was seen at 24 hours when 2 minutes of exposure resulted in a burn leading to a scar. The maximum sensitivity due to *SC102* was seen up to 2 weeks when up to 16 minutes of exposure caused transient erythema only. In keeping with clinical experience, burns were seen with *mTHPC* whereas at an equivalent tumoricidal dose, *mTHPC-PEG* caused erythema.

Conclusions: The new photosensitiser *SC102*, at a potentially effective dose, causes less cutaneous photosensitivity than the established photosensitiser *mTHPC* and may lead to better acceptance of photodynamic therapy.

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Evaluation of the Photosensitizing Third Generation Drug SC 102 aka Tetrakis-(methoxypolyethylene glycol [MW 2000]) in Two Animal Models.

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The third generation compound SC 102, a derivative of Foscan® (temoporfin, m-THPC) was evaluated for photodynamic efficacy utilizing two animal models: the rabbit inoculated with the cottontail rabbit papilloma virus (CRPV) and the healthy canine larynx. The study was designed as a direct comparison to our earlier study with Foscan® and was divided into two distinct parts. First, the optimal treatment interval was sought by measuring plasma and tissue uptake and retention kinetics. The second part sought to define the optimal light and drug dose for best treatment efficacy with the optimal interval. The first study included two groups of four Dutch-belted rabbits, the first group injected with 3 mg/kg SC 102 and the second with 30 mg/kg. Each group was inoculated with the CPRV virus and tumors were allowed to grow for 2-4 weeks to a manageable size ranging from 2-4000 mm^3. Tumors, healthy surrounding tissue and plasma pharmacokinetics were then measured as a function of time. Plasma pharmacokinetics showed a half life of 121 hours while tumor uptake maximized at 144 hours for the 3 mg/kg group. Surrounding skin showed no peaking but rather a steady accumulation of 200 ng/ml for a period of 2 weeks. Both tumor and healthy surrounding skin peaked at 240 hours for the 30 mg/kg group. Tumor to healthy tissue ratios were approximately 4 to 1 in both cases. The second phase of the study utilized a group of 4 additional Dutch-belted rabbits each inoculated in 15 locations with the CRPV virus which were allowed to grow for 4 weeks to a manageable size of 2-4000 mm^3. These animals were treated with 652 nm light at 100 mw/cm^2 at 6 and/or 10 days post injection as follows: 2 rabbits (26 tumors) were treated with 75 Joules/cm^2 on day 6 and then again with the same dose on day 10. The second group of 2 (21 tumors) were treated on day 10 with 100 Joules/cm^2. The single treatment group showed a 35% cure rate while the group treated on day 6 and 10 showed a 58% cure rate. An additional group of 2 rabbits were tested for photosensitivity after a drug dose of 30 mg/kg was administered by irradiating with a variety of laser fluences at various times ranging from few minutes to 10 days and from 5 Joules/cm^2 to 160 Joules/cm^2. Skin showed no damage even at fluence levels of 160 Joules/cm^2. The larynx study was initiated with the accepted model of healthy mongrel dogs 7.5-10 kg. They were given a dose of 30 mg/kg and were exposed to a range of 100-400 Joules total with 652 nm light delivered via a 3cm fiber diffuser at a flux of 100 mw/cm^2. The drug light interval was 10 days and damage was evaluated on day 11.

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LASER CHEMOTHERAPY FOR TREATMENT OF HUMAN SOLID TUMORS. R. E. Saxton, M. B. Paiva, I. P. Graeber, W. H. Paek, M. J. Suh, and D. J. Castro. Department of Surgery, UCLA School of Medicine, Los Angeles California, USA; and (IPG), Department of Head and Neck Surgery, Benjamin Franklin Hospital, Free University of Berlin, Berlin, Germany.

Purpose: Combined intratumor drug and laser treatment were tested as a new approach for therapy of human solid tumors. Methods: Cisplatin and an anthracycline-related drug (Dup-941) were injected separately into 300-500mg human squamous cell carcinoma (SCCA) tumors grown as subcutaneous transplants in nude mice. After 4 hours to allow intratumor drug diffusion, SCCA transplants were exposed to photothermal energy delivered interstitially via 0.6mm fiberoptics from a KTP/Nd:YAG laser (300J at 532m). Results: Comparison of the combined therapy cohort with drug or laser alone control groups revealed improved outcome after Dup-941 and KTP laser treatment. SCCA tumor recurrence after laser chemotherapy was reduced to 8/29

compared to 16/29 ($0.02<p<0.03$ by x^2) for laser ablation alone. Drug alone at 0.060-1.2 mg/gm tumor induced delayed growth at the highest dose, but no complete regressions were observed during 8-20 weeks followup. Similar intralesional injection of cisplatin at escalating doses of 0.38, 0.75, or 1.13 mg/gm tumor in 13 SCCA transplants led to progressively decreased growth compared to untreated controls. Cisplatin injected at these doses in slow release gel further retarded SCCA tumor growth in 16 mice without complete regression in any case. By contrast, recurrence was seen in only 2 of 8 SCCA tumors after combined cisplatin gel and KTP laser treatment. Conclusions: Interstitial drug and laser photothermal therapy were an effective combined treatment in these preclinical tumor studies. Further testing of efficacy and toxicity will be needed before evaluation in cancer patients.

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KINETICS AND MECHANISM OF 5-AMINOLEVULINIC ACID-BASED PHOTODYNAMIC THERAPY FOR BARRETT'S ESOPHAGUS.

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Barrett's epithelium is a premalignant lesion, with a 40-fold increased risk of developing adenocarcinoma in the esophagus. Photodynamic therapy (PDT) with 5-aminolevulinic acid (ALA)-induced photosensibilisation may be used to selectively eliminate Barrett's epithelium. To find optimal treatment parameters, the kinetics, localization and mechanism of ALA-induced Protoporphyrin IX (PpIX) accumulation in a rat model for Barrett's esophagus were studied.

To induce Barrett's esophagus, an esophagojejunostomy was performed in 48 rats. Eighteen weeks later, these animals and 48 control animals received 200 mg/kg ALA i.v. or p.o.. At t=0,1,2,3,4,6,12, and 24 hours after ALA administration, porphyrin concentrations in the esophagus were measured using confocal laser scan microscopy (CLSM) and a quantitative chemical extraction method. Additionally, in the esophageal wall of 20 rats, two enzymes of the haem synthetic pathway (porphobilinogen deaminase (PBGD) and ferrochelatase) and iron concentration were determined to analyse the mechanism of selective ALA-induced porphyrin accumulation.

Using CLSM, strong homogeneous fluorescence of the basal cell layer of the squamous epithelium lining the normal rat esophagus was found, whereas fluorescence of the submucosa and muscularis was at background levels. In both the p.o. and i.v. group fluorescence intensity increased until 3 hours after ALA administration, thereafter fluorescence decreased. In rats with Barrett's esophagus, fluorescence of the Barrett's epithelium was more heterogeneous and also restricted to the mucosal layer. No selectivity of PpIX accumulation of Barrett's epithelium in favour of squamous epithelium was detected. With the chemical extraction method, porphyrin accumulation in mucosa was approximately 3.5 fold higher than in the muscularis, with a maximum at 3 hours after ALA administration. Results of the i.v. and p.o. group were comparable. Results of the CLSM and chemical extraction methods were supplementary. Enzyme measurements showed a higher activity of PBGD in the mucosa compared to the muscularis ($p<0.0001$). No difference in ferrochelatase activity was found between the two layers of the esophageal wall. Iron concentration in the esophageal mucosa was lower than in the muscularis ($p<0.001$).

In conclusion, in the rat esophagus, ALA-induced endogenous production of PpIX selectively occurs in the mucosa, with peak levels at 3 hours after ALA administration. A possible explanation for this selective accumulation is a higher ratio of PBGD:ferrochelatase in the mucosa and a relative low iron concentration. This makes ALA most suitable for PDT treatment of Barrett's esophagus.

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LASER INDUCED FLUORESCENCE ENDOSCOPY (LIFE) DURING PHOTODYNAMIC THERAPY (PDT) FOR ESOPHAGEAL CANCER.

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Purpose: The purpose of this study was to measure photosensitizer (PS) levels in normal and malignant esophageal tissue before and after palliative PDT in order to assess PS concentration and selectivity, and the effectiveness of PS activation by light (a potential predictor of cytotoxic substance generation and necro-inflammatory response). **Methods:** Four esophageal cancer patients scheduled for palliative PDT were given 1 to 2 mg/kg IV Photofrin®. PDT was performed 6 h after the 1 mg/kg dose and 48-72 h after the 2 mg/kg dose. Immediately before PDT real-time LIFE images, point spectroscopy and standard mucosal biopsies were taken from 2 sites in normal and 3 sites in malignant mucosa. At least 5 spectra were collected from each interrogated mucosal site, detected with an optical multichannel analyzer, and normalized to 750 nm during data analysis. Biopsies obtained from the same sites were processed for subsequent *ex situ* fluorescence quantification by chemical extraction. The tumor was then exposed to 630 nm light from an argon dye laser (delivered via a cylindrical diffusing tip) for a total light dose of 300 J/cm. Immediately after PDT, LIFE images, point spectroscopy, and biopsies were again taken from normal and malignant sites. This sequence was repeated 48 hours later at the time of a second application of laser light. **Results:** Real-time LIFE images after delivery of each light dose showed a marked decrease in fluorescence intensity in malignant (compared with normal) areas suggesting photobleaching and potential PS photoactivation. Tissue extraction data [average μg/g/dose ± SD]:

Specific Uptake Ratio	Pre-PDT1	Post-PDT1	Pre-PDT2	Post-PDT2
Normal	1.30 ± 0.40	1.37 ± 0.39	1.41 ± 0.38	1.69 ± 0.60
Tumor	3.09 ± 2.30	3.14 ± 1.43	5.29 ± 6.16	2.39 ± 1.40

showed a 2.5-fold greater PS selectivity for tumor and a large variability in porphyrin concentration. Analysis of the area under the spectral curves confirmed the extraction results. **Conclusions:** PS levels accumulate selectively in malignant esophageal mucosa compared to normal mucosa. After PDT, tissue PS measurement by spectroscopy and chemical extraction may be influenced by endogenous porphyrin generation or intratumor oxygenation or uptake variability. However, real-time LIF endoscopy detects a qualitative decrease in malignant tissue fluorescence levels indicating photochemical activation of the PS and, indirectly, the degree of photobiologic (cytotoxic) effect. LIFE may be a practical clinical adjunct for dosimetry in PDT.

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Photodynamic therapy of malignant ovarian tumors cultivated on CAM

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Abstract

The disappointing results with either surgery alone and/or chemotherapy in the treatment of malignant ovarian tumours have led to an increased interest in additional treatment schedules. Photodynamic therapy (PDT), a modality involving the use of a photosensitizing drug and activating light, is being used increasingly as a local treatment for neoplastic lesions. The synthesis and evaluation of new photosensitizers for the treatment of gynaecological lesions and malignancies continues to be an active area of investigation for proper application of the photodynamic process in gynaecological field. The effect of PDT using methylen blue (free and combined with liposomes) as a photosensitizer for treating human ovarian malignant tumours cultivated on the CAM was evaluated. Two days after PDT, the treated implanted tumours were markedly decreased in size. Areas of necrosis with black coloration, dryness and eschar formation were observed. Five days after PDT, tumours remission were clearly observed in all the treated tumours. Photodynamic therapy using MB (aqueous and coupled with liposomes) is effective for treating the ovarian malignancies and it will be capable of achieving complete eradication of visible tumours in patients with superficial lesions.

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PHOTOCHEMOTHERAPY OF SUPERFICIAL HEAD AND NECK CANCER : A PROSPECTIVE STUDY OF 16 PATIENTS

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The authors analyse the result of laser photochemotherapy on 16 patients who had presented a superficial squamous cell carcinoma T1 or T2N0M0 of the oral cavity, pharynx and larynx.

In this prospective study, started in 1990, photochemotherapy was suggested as a curative treatment. After photosensitizing with hematoporphyrine derivative (photophrin), an Argon dye Laser (632nm) delivered a fluence (energy density) of 275 J/cm2.

In our series, 75% of the patients showed complete clinical remission with an excellent functional result. 25% did not respond to the treatment and biopsies were positive one month after laser exposure. Thus, they underwent a classical treatment and are now in complete clinical remission.

The results suggest that laser photochemotherapy is a useful treatment for small superficial tumors and in case of non-response has no adverse impact on the efficacy of the classical treatment.

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PHOTOCHEMOTHERAPY OF ADVANCED HEAD AND NECK CANCER A PROSPECTIVE CLINICAL STUDY

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The authors present a prospective study begun in 1990, discussing their result of laser photochemotherapy on 8 patients with advanced head and neck carcinomas.

These patients had presented a recurrence of their advanced carcinoma after a classic treatment (surgery or radiotherapy), photochemotherapy was suggested as a palliative treatment. After photosensitizing with hematoporphyrine derivative (photophrin) or Adriamycine, an Argon dye Laser (632nm) delivered a fluence (energy density) of 215 J/cm2.

In our series, 62% of patients responded to the treatment showing "partial tumor regression" or "clinical improvement".

Our results suggest that laser photochemotherapy is an attractive alternative for treatment of advanced or recurrent head and neck tumors in cancer patients.

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Direct Interaction of Light with Cells in Photodynamic Therapy

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Liu TCY et al ('low intensity laser biostimulation', this proceedings) have put forward the biological information model on low intensity light (BIML): low intensity light couples with intracellular messenger through the chromophore absorption in the cell membrane: hot-color (red, orange, yellow) light activates cAMP phosphodiesterase through G_i protein or activates phosphoinositide phospholipase C through G_q protein, or activates one of receptor-associated kinases: cAMP↓; cold-color (green, blue, violet) light activates adenylate cyclase through G_s protein: cAMP↑. In this paper, we applied BIML to studying the direct interaction of light with cells in photodynamic therapy. It was concluded that cold color light PDT is better than hot color light PDT from the viewpoint of the effects on cells and the short term effects on cancer, but hot color light PDT is superior to cold color light PDT with respect to the long term effects on cancer.

PLASTIC SURGERY/ DERMATOLOGY

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LONG PULSE 532nm LASER TREATMENT OF LOWER EXTREMITY TELANGIECTASIAS A CLINICAL AND HISTOLOGIC STUDY

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At the present time the use of lasers in the treatment of leg veins remains a controversial and problematic area. Although many lasers are capable of improving and eradicating facial telangiectasias, it appears that leg veins are more resistant to currently available laser treatments. Recently a Long-Pulse 532nm Neodymium-YAG laser (VersaPulse^R, Coherent Medical, Palo Alto, CA) has been introduced for the treatment of facial blood vessels, port wine stains and leg veins. In an attempt to delineate the role of this laser in the treatment of leg veins, we studied one hundred patients with telangiectatic vessels of the lower extremities ranging from 0.4mm to 1.5mm. Simultaneously we conducted a histologic examination of leg veins during laser treatment by obtaining biopsies preoperatively, immediately postoperatively, at 5 days and at 3 weeks. The results of our study indicate that the VersaPulse^R laser

is capable of eliminating a significant percentage of leg veins within one or two treatments. Our histologic studies show remarkable vascular endothelial changes with necrosis, thrombosis with subsequent vessel fibrosis. The results of our clinical and histologic studies indicate that this laser shows promise in the treatment of lower extremity telangiectasias.

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COMPARISON OF THE 595 nm LONG-PULSE (1.5 ms) AND THE 595 nm ULTRA-LONG PULSE (4 ms) LASER IN THE TREATMENT OF LEG VEINS

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Although several lasers and light sources are now available for vascular lesions, treatment of leg veins has not been very satisfactory. Lengthening the pulse width should theoretically result in improved response rates. The purpose of this study was to compare the efficacy and safety of 595 nm pulsed lasers at 1.5 msec and 4 msec in treating leg veins.

Twenty-seven healthy adult volunteers with leg veins measuring less than 1 mm in diameter were treated with a 2 x 7 mm elliptical handpiece. Each patient had 3 areas treated. One was treated with the 1.5 msec pulsed dye laser at fluences ranging from 14-16 J/cm^2 and the remaining 2 areas with the 4 msec pulsed dye laser with fluences of 16 J/cm^2 and 20 J/cm^2 respectively. Clinical evaluations were performed and photographs taken at 4-6 week intervals and re-treatment was performed at least 8 weeks after the initial treatment using the same parameters.

Preliminary data show that neither laser regularly induced satisfactory diminution or disappearance of these vessels after one treatment. Aside from transient hyperpigmentation, no adverse effects were observed. The 4 msec laser did not show any significant advantage over the 1.5 msec laser.

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DIODE LASER TREATMENT OF LEG VEINS.

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Ectatic leg veins are currently being treated by either sclerotherapy or several laser and a non-laser light source. All of these modalities are variably reliable, occasionally being effective with tolerable side effects and other times of no benefit to the patient. In the pursuit of developing a more predictable approach to the treatment of leg veins, a diode laser at 810 nm was evaluated. Twelve patients with a total of 58 treated vessels having a vessel diameter from 0.3 to 0.5mm were studied. Laser parameters were set at 40W, a pulse duration of 40 to 50msecs and a spotsize of 0.75mm. There was no immediate post-operative bruising or blackening instead the vessels commonly became erythematous and edematous. The vessels responded with a mean clearance after 2.2 treatments of 60.5%. There appears to be greater lightening with more treatment sessions up to 70% response after three treatments. Only occasional hyperpigmentation occurred in a few vessels. The diode laser may offer leg vein patients a therapeutic approach which is relatively effective with minimal adverse effects at the studied parameters. Optimizing the laser parameters further, may result in even greater effectiveness.

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NON-COHERENT FILTERED FLASHLAMP INTENSE PULSED LIGHT SOURCE FOR LEG TELANGIECTASIAS: LONG PULSE DURATIONS FOR IMPROVED RESULTS

Robert A. Weiss, Margaret A. Weiss, Sangeeta Marwaha, Allan C. Harrington, Johns Hopkins U School of Medicine, Baltimore, MD. The purpose was to study new parameters for more effective treatment of leg telangiectasias than previously reported using IPLS. Recommended parameters have included pulses on the average of 3 msec with fluences no greater than 35-40 J/cm2. These have resulted in response rates of approximately 50% after an average of three to five treatments. For our study, 40 sites on 20 consecutive patients were treated with a progressive set of pulse widths. Treatment results were evaluated at 2-4 week intervals and clearance rates estimated by comparison photographs.

Initial parameters included both a short and long pulse of 2.4 msec and 6 msec at 40J/cm2 with 570nm cutoff filter, separated by a 10 msec thermal relaxation interval. Visual endpoints included complete darkening of the targeted vessel(s) with a 2 mm or greater urticarial flare within 10 minutes. When this endpoint was not seen, pulse durations to adjacent sites were increased to a maximum of 9.5 msec for two consecutive pulses separated by a 20 msec thermal relaxation time (570nm cut-off filter) with total fluences of up to 70 J/cm2. Response rates (90% clearance) increased to (31/40) 78% with three treatments. Incidence of adverse reactions included a mild burning sensation lasting less than 10 minutes noted in 45%. Most importantly, no cases of epidermal injury were observed. Short-term hyper- or hypo- pigmentation (< two months) was noted in approximately 8% of sites treated. Use of long pulses with the intense pulsed light source allows more effective treatment for leg telangiectasias. Cutaneous side effects are reduced.

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COMPARISON OF SIX ERBIUM:YAG LASERS FOR CUTANEOUS RESURFACING: A CLINICAL AND HISTOPATHOLOGIC EVALUATION

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PURPOSE: To determine the histologic and clinical effects of six different erbium:YAG lasers for cutaneous resurfacing.

METHODS: Full facial resurfacing of 12 patients was performed using six different erbium:YAG lasers (Candela, ConBio, HGM, MDLT, SEO, Sharplan) at equivalent laser parameters. Skin

punch biopsies were performed after 1, 2, and 3 laser passes with each laser system. Blinded clinical evaluations by two independent assessors were performed from sequential photographs obtained at baseline, 0.5, 1, 2, 4, and 12 weeks postoperatively.

RESULTS: Variable histologic depths of tissue ablation were observed between the different erbium:YAG laser systems. No significant clinical differences were observed in terms of re-epithelialization rates, duration of erythema, or clinical outcome. Complication rates after laser resurfacing were equivalent after resurfacing with each laser.

CONCLUSION: Similar clinical results can be obtained using the different erbium:YAG lasers currently available for cutaneous resurfacing. Differences in histologic findings between the six systems studied were observed after 1, 2, and 3 laser passes.

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TREATMENT OF NECK AND HAND PHOTOAGED SKIN WITH THE ER:YAG LASER. David J. Goldberg, Skin Laser Center, Pascack Valley Hospital, Westwood, NJ.

This study was undertaken to determine efficacy and complication rate when the Er:YAG laser is used for non-facial photoaged skin. 15 subjects, Fitzpatrick skin phenotypes I-III, with photoaged neck and hand skin were entered into the protocol. All individuals were treated with a 2940 nm, 300 usec pulsed, Er:YAG laser. All areas were treated with 4-6 passes and a fluence of 4-5 J/cm^2. Subjects, followed for six months after treatment, were evaluated both objectively and subjectively for degree of improvement and incidence of scarring and post-inflammatory pigmentary changes. A greater degree of improvement in color and textural changes was noted as compared to actual rhytid improvement. No subjects had any adverse pigmentary changes or scarring at six months. The Er:YAG laser is efficacious in improving non-facial photoaged skin.

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LASER RESURFACING OF THE NECK AND HANDS USING THE Er:YAG LASER. Mitchel P. Goldman, Richard E. Fitzpatrick, Yardy Tse, San Diego, CA.

Purpose: The purpose of this study was to evaluate the efficacy of the Er:YAG laser in the treatment of rhytides and dermatoheliosis of the neck and hands.

Method: 20 patients with photo-damaged skin of the neck and dorsa of the hands were treated with the Er:YAG laser. The neck, from the mandible to the sternal notch, was treated with 1-3 passes, using fluences of 6 to 24 J/cm^2. One to eight passes of the Er:YAG laser and fluences of 6 to 24 J/cm^2 was used to treat the dorsa of the hands. Clinical improvement was assessed by pre- and post-operative photographs at follow-up periods of 6 to 12 months.

Results: Skin color and texture improved in all patients. Re-epithelialization was rapid, occurring in 5-10 days in all patients, and erythema resolved in 2-3 weeks in most patients. There was no scarring, or persistent hyper- or hypopigmentation. A few isolated macules of hypopigmentation were rarely seen.

Conclusions: The Er:YAG laser is safe and effective in treating photodamaged skin of the neck and hands.

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ERBIUM:YAG LASER RESURFACING: A CLINICAL HISTOPATHOLOGIC EVALUATION

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Erbium:YAG laser treatment is a new modality being used for facial skin resurfacing. The purpose of this presentation is to discuss the clinical efficacy and side effects of Erbium:YAG laser resurfacing, and its relative advantages and disadvantages compared to CO_2 laser resurfacing. The progression of wound healing following Erbium:YAG laser treatment has also been studied with particular attention to the effects on collagen and elastic tissue.

Ten patients were treated with full face Erbium:YAG laser resurfacing, utilizing fluences of 1.5 to 2.0 J/cm^2. Patients were treated with either 3, 6 or 9 passes of the Erbium:YAG laser, depending on the severity of photo damage.

Time to re-epithelialization and side effect profile, including post-treatment erythema, pain, infection, pigmentary change and scarring were noted. In order to assess the progression of wound healing, pre-treatment biopsies, as well as post-treatment biopsies at 1 week, 6 weeks, 12 weeks and 24 weeks, were evaluated for progression of re-epithelialization, and changes in collagen and elastic tissue.

The clinical and histological effects of Erbium:YAG laser resurfacing of rhytides and photodamaged skin are discussed. The relative advantages and disadvantages of skin resurfacing with the Erbium:YAG laser compared to the CO_2 laser are presented, as well as the long-term histopathologic effects on

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ERBIUM:YAG LASER RESURFACING FOR MELASMA

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PURPOSE: Melasma is a common complaint in patients with darker skin tones. Many therapies for this condition are ineffective and can cause significant adverse effects. The purpose of this study was to evaluate the role of erbium:YAG laser resurfacing in the management of melasma.

METHODS: Ten female patients with melasma were enrolled in the study. Full face skin resurfacing using an erbium:YAG laser (2.94μm) was performed using identical laser and postoperative protocols in each patient. Clinical evaluations and melanin reflectance spectrometry measurements were taken preoperatively and at 0.5, 1, 1.5, 3, 6 and 12 weeks postoperatively. Adverse effects after laser resurfacing such as prolonged erythema, infection and hyperpigmentation were recorded.

RESULTS: There was significant improvement in the overall skin tone and color in all treated patients. A decrease in clinical pigmentation was observed and objectively demonstrated by reflectance spectrometry.

CONCLUSIONS: Cutaneous resurfacing with the erbium:YAG laser can effectively improve the appearance of melasma.